6. SERIOUS ADVERSE EVENT REPORTING

6.1 Background

The purpose of this document is to acquaint site personnel to the DCP requirements for identifying, documenting, and reporting SAEs for the MAH phase I and II studies. Further, this document provides orientation to the roles and responsibilities of the site, DCP personnel, and DCP contractors.

Adverse Events (AEs) are untoward clinical events experienced by a study participant while taking part in a clinical trial. Such events may be abnormal laboratory values or physical signs or symptoms. An AE becomes a SAE when it results in any one of the following outcomes:

- Death;
- Life-threatening event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- A congenital anomaly/birth defect; or
- An important medical event that may not result in death, be life threatening, or require hospitalization, though, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the previously identified outcomes.

NOTE: Grade 3 events (per NCI Common Toxicity Criteria Version 2.0 and 3.0) that fit the above criteria will be treated as SAEs. These can be found at http://ctep.info.nih.gov/reporting/CTC-3.html. **All** Grade 4 events will be considered SAEs.

DCP has hired a company to provide technical and regulatory support to the division. This contractor, CCS Associates (CCSA) of Mountain View, California, assists DCP in assessing, tracking, and reporting SAEs.

6.2 Site's Responsibility in Reporting SAEs to DCP

In the interest of participant safety in DCP studies, and to fulfill regulatory requirements, **all** SAEs, *whether related to the study agent or not*, will be reported to the sponsor (NCI/DCP) as follows:

- Contact the DCP Medical Monitor by telephone or fax within 24 hours of learning of the SAE. When calling or faxing, please include date, time, your name, phone number, affiliation, reason for calling/faxing, NCI contract, and protocol number.

- Submit a written report within 48 hours of the PI learning of the event.

  - The written information shall be documented on the "NCI Division of Cancer Prevention Serious Adverse Event Form."

  - The SAE Form is available in Appendix C and/or http://www3.cancer.gov/prevention/pio/instructions.html

  - Send the completed form to the DCP Medical Monitor as indicated in the protocol document.

  - Simultaneously submit the form to CCSA:

    Kathleen Dolan, RN, MS
    CCS Associates, Inc.
    2005 Landing Drive
    Mountain View, CA 94043
    Kdolan@ccsainc.com

    Note: Do not delay sending the form if all pertinent information is not available within the 48 hour window. Send the form with as much information as possible and update the form with the DCP Medical Monitor and CCSA as additional information becomes available.

- All SAEs must be entered in the AE CRF.

- All SAEs are listed in the "Cumulative Adverse Event" section of the "Investigator Technical Progress Report" http://www3.cancer.gov/prevention/pio/instructions.html.

- The PI must report all SAEs to the local IRB according to institutional guidelines.

6.3 DCP Processing and Reporting Responsibility to FDA

In its role as IND sponsor, NCI/DCP is required to review and analyze all SAE reports for impact on participant safety in the study. The DCP Medical Monitor immediately reviews all SAEs to

determine if the event is related to the study agent and is unexpected. If the Medical Monitor determines that these criteria exist, the FDA requires the IND sponsor to file an expedited report to the FDA as soon as possible but no later than 15 days after the event is reported. If the event is unexpected and fatal or life-threatening and associated with the use of the study agent, then the FDA must be notified as soon as possible but not later than 7 calendar days after the initial receipt of the information. This report, known as an "IND safety report," will be circulated to all investigators participating in trials using the agent. CCSA assists the Medical Monitor by ensuring that all required information is obtained from the site and performs as a liaison with the FDA. See Figure 6-1 for the SAE reporting process.

6.4 SAEs and Site Monitoring

- During a site visit, the DCP/Westat CRA will ensure that site staff have:
  - Verifiable source documentation to support the SAE;
  - Appropriately filed the SAE documentation with DCP and CCS Associates;
  - Recorded the SAE on the appropriate CRF; and
  - Notified the local IRB.
- If the CRA identifies any unreported SAEs during a monitoring visit, the site staff will report and document the information with guidance from the CRA.

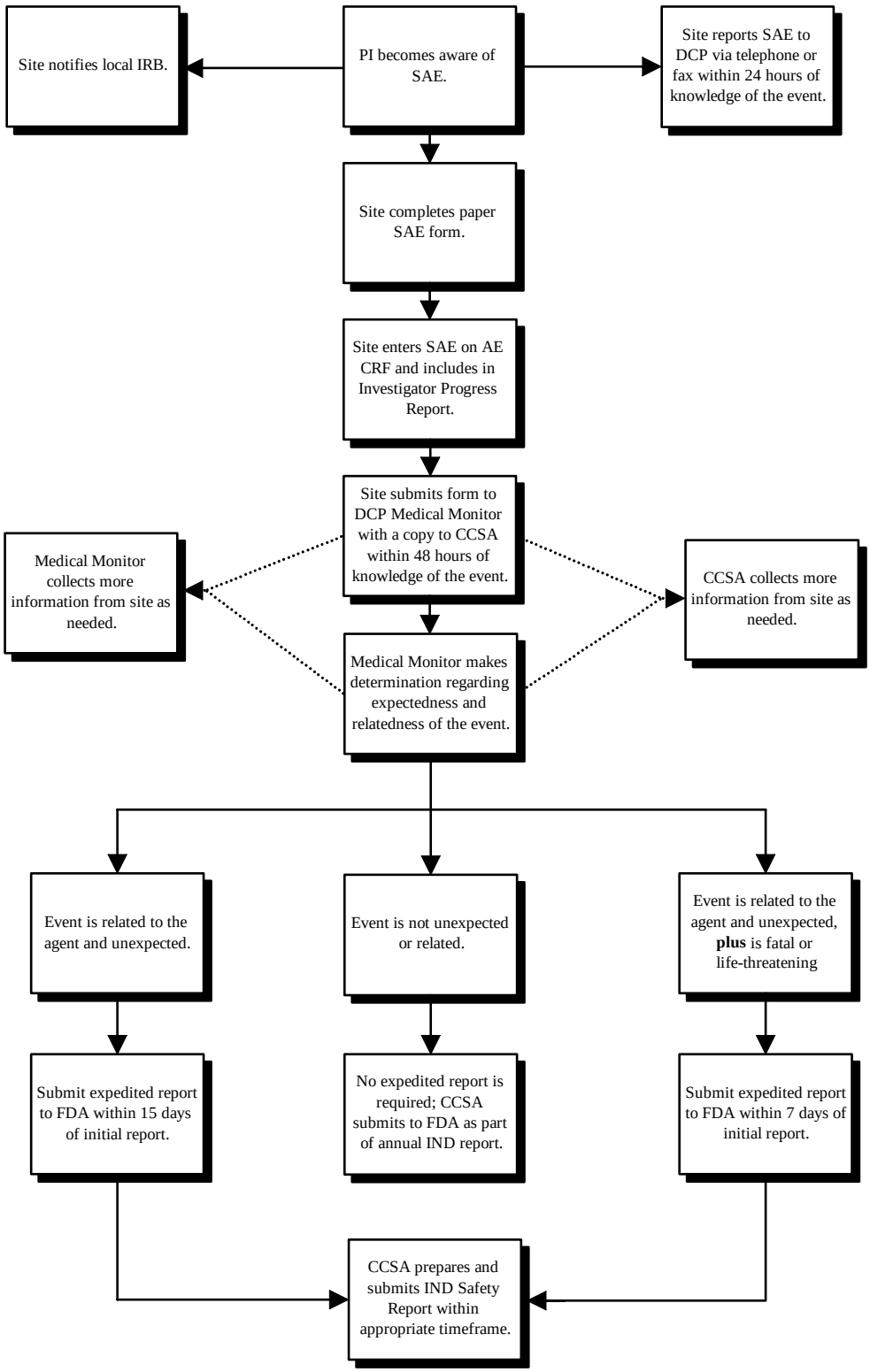

Figure 6-1. SAE reporting process